SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

Summary of Safety and Effectiveness Data

I. General Information

Device Generic Name:	Vascular Hemostasis Device
Device Trade Name:	EVS™ Vascular Closure System
Applicant:	*angio*LINK Corporation 125 John Hancock Road, Suite Six Taunton, MA 02780

Premarket Approval Application (PMA) Number: P040022

Date of Panel Recommendation: None

Date of Notice of Approval to Applicant: November 3, 2004

II. Indications for Use

The EVS™ Vascular Closure System is indicated for percutaneous femoral artery approximation. The EVS™ Vascular Closure System is also indicated to reduce time to hemostasis at femoral puncture sites and to reduce time to ambulation for patients undergoing diagnostic and interventional catheterization procedures using 6 – 8 French procedural sheaths.

III. Contraindications

There are no known contraindications for the EVS ™ Vascular Closure System.

IV. Warnings and Precautions

The Warnings and Precautions can be found in the EVS ™ Vascular Closure System labeling.

V. Device Description

A. Materials and Configuration

The EVS™ Vascular Closure System (EVS or EVS device) delivers a titanium staple extravascularly to a femoral artertiomy access site. The device comes to the user packed in a thermoform tray with a Tyvek™ lid. Inside the tray, there is a stapler and introducer/dilator assembly. The key components of the EVS are described below with respect to each component:

1) The Stapler is a hand activated device for staple delivery, closure, and release.
2) The Staple is made of a biocompatible 3AL 2.5V titanium alloy.

3) The Introducer/Dilator Assembly has the following subcomponents:

The introducer is the introducing tube that allows the dilator and the stapler to pass through the skin, fascia, and soft tissue, acting as a conduit to the arteriotomy. As part of the Introducer/Dilator Assembly, there are several sub-components that maximize location and stabilization of the targeted vascular arteriotomy.

1. On the Introducer, an activation mechanism deploys stabilization feet intraluminally to control the arteriotomy and gently secure the Introducer to the inside and outside of the arteriotomy puncture site.

   The stabilization feet retract, with controlled compression, to the inside wall of the targeted vessel towards the distal end of the introducer. The stabilization feet control the wound site during insertion of the stapler into the Introducer and delivery of the Staple into the wall of the vessel.

2. On the outside of the Introducer is a transition over-sheath, which is a lubricious covering that eases the transition between the introducer and dilator. This minimizes tissue trauma while tracking to the wound site, and reduces "snag-points" while guiding the Introducer to the center of the arteriotomy.

3. The dilator of the Introducer/Dilator Assembly enables the device to track over and follow the path of the guidewire to the arteriotomy. The dilator centers the introducer at the wound/puncture site and stores the stabilization feet before deployment/activation.

B. Principles of Operation for the EVS™ Vascular Closure System:

The EVS was designed to percutaneously repair a puncture hole that was created in the accessed blood vessel after a percutaneous cardiac and/or peripheral catheterization procedure has been performed.

The EVS is used following percutaneous femoral catheterization procedures. These procedures are performed to diagnose and/or treat completely or partly occluded vessels within the body. During these procedures, an introducer/sheath is placed percutaneously into the femoral artery. Using this sheath or introducer, a series of instruments can be inserted into the vascular system. Following the catheterization procedure, a guidewire is reintroduced through the introducer and the introducer sheath is removed. The puncture or arteriotomy is then closed by advancing the EVS device (the dilator and introducer as a single unit) over the guidewire through the skin and soft tissue into the arteriotomy until brisk blood response from the dilator arterial marking lumen is achieved. The dilator is then further advanced over the guidewire, freeing and deploying the stabilization feet intraluminally against the interior wall of the artery.

At this point, the dilator and guidewire are removed from the introducer and the stapler is advanced through the introducer and locked into place.

The staple is then deployed by squeezing the trigger. After the staple is deployed by activating the trigger, the stabilization feet are un-deployed and the entire device is removed.

VI. Alternative Practices and Procedures

Alternative practices for achieving hemostasis of the femoral artery puncture site post-catheterization include manual compression, mechanical compression, collagen-based hemostasis devices, and percutaneous delivery of sutures to the femoral artery access site. Pressure dressings and sandbags are routinely used in combination with compression methods to control oozing.

VII. Marketing History

The EVS has not been marketed in the United States or any foreign country.

VIII. Potential Adverse Effects of the Device on Health

The EVS was evaluated in a pivotal, prospective, multi-center, open-label, randomized study involving 362 patients. The EVS was compared to Manual Compression (MC) methods following interventional and diagnostic cardiac and peripheral vascular procedures with 8 Fr or smaller sheath sizes. Of the 362 patients, 243 (67%) patients were randomized to the EVS™ Vascular Closure System and 119 (33%) patients were randomized to MC. Randomized EVS patients were approximately evenly divided between procedure groups: 118 (49%) had interventional procedures and 125 (51%) had diagnostic procedures.

Patients who were randomized to the EVS device were asked to ambulate at pre-set time intervals after the diagnostic/interventional procedure was complete. EVS patients without glycoprotein IIb/IIIa inhibitors were ambulated at 1 hour, while patients with IIb/IIIa inhibitors were ambulated at 2 hours. MC patients without IIb/IIIa inhibitors attempted ambulation at 4 hours and MC patients with IIb/IIIa inhibitors attempted ambulation at 6 hours.
The study was designed to detect a difference in the observed incidence of major complications at 30 days. Assuming a 3% cumulative major complication rate for manual compression, the study was designed to rule out a 5% higher major complication rate for the randomized EVS group. The sample size was adequate to rule out a 5% EVS disadvantage using a 95% upper confidence bound.

The EVS device demonstrated safety. By Day 30, a cumulative total of 1 (0.4%) major complication was reported for randomized patients who received EVS, compared to 3 (2.5%) major complications in the manual compression patients. The differences in rates of cumulative major complications between the EVS and MC groups were not statistically significant at Day 30 (1.1%, 95% exact one-sided upper confidence bound).

Rates of minor complications were low and similar between the two randomized treatment groups (8.7% for EVS at Day 30 and 8.3% for MC). Minor complications were correlated with pre-closure Activated Clotting Time (ACT) levels; minor complications

occurred at lower rates in subjects with lower ACT levels. Similarly, minor complication rates were lower in subjects without IIb/IIIa inhibitors and in subjects undergoing diagnostic as opposed to interventional procedures. The most common minor complication was ecchymosis. When randomized subjects whose only minor complication was ecchymosis were removed from the analyses, the cumulative rates of minor complications at Day 30 were 6.2% (randomized EVS subjects), and 5.8% (MC subjects).

Table 1: Cumulative Anticipated Major and Minor Complications (ITT Population)

	Received EVS (N=243)		Received MC (N=119)		Fisher's Exact Test P-value[1]
	No. (%) of Patients	No. of Events	No. (%) of Patients	No. of Events	
Combined major complications at Day 30[2]	1 (0.4%)	1	3 (2.5%)	3	0.1058
Retroperitoneal bleeding	1 (0.4%)	1	1 (0.8%)	1	0.5500
Uncontrolled bleeding requiring transfusion	0 (0.0%)	0	1 (0.8%)	1	0.3287
New ischemia in ipsilateral leg	0 (0.0%)	0	1 (0.8%)	1	0.3287
Ultrasound guided compression for vascular surgery	0 (0.0%)	0	0 (0.0%)	0	
Vascular Surgery	0 (0.0%)	0	0 (0.0%)	0	
Intraluminal staple delivery requiring surgical intervention	0 (0.0%)	0	0 (0.0%)	0	
Groin related infection requiring IV antibiotics or extended hospitalization	0 (0.0%)	0	0 (0.0%)	0	
New significant neuropathy in ipsilateral lower extremity	0 (0.0%)	0	0 (0.0%)	0	
Total Vessel Occlusion	0 (0.0%)	0	0 (0.0%)	0	
Combined minor complications at Day 30	22 (9.1%)	31	9 (7.6%)	13	0.6941
Uncontrolled bleeding not requiring transfusion	3 (1.2%)	3	3 (2.5%)	3	0.3992
Hematoma ≥6cm	9 (3.7%)	11	4 (3.4%)	5	1.0000
Ecchymosis >3mm	11 (4.5%)	11	5 (4.2%)	5	1.0000
Intraluminal staple delivery not requiring surgical intervention	1 (0.4%)	1	0 (0.0%)	0	1.0000
Pseudoaneurysm not requiring treatment	3 (1.2%)	3	0 (0.0%)	0	0.5538
Pseudoaneurysm requiring thrombin injection	2 (0.8%)	2	0 (0.0%)	0	1.0000
Pedal pulse diminished by ≥ 2 grades	0 (0.0%)	0	0 (0.0%)	0	
Ipsilateral lower extremity arterial emboli	0 (0.0%)	0	0 (0.0%)	0	
Ipsilateral deep vein thrombosis	0 (0.0%)	0	0 (0.0%)	0	
Access site-related vessel laceration	0 (0.0%)	0	0 (0.0%)	0	
Access site wound dehiscence	0 (0.0%)	0	0 (0.0%)	0	
Localizes access site infection treated with intramuscular or oral antibiotics	0 (0.0%)	0	0 (0.0%)	0	
Arteriovenous fistula	0 (0.0%)	0	0 (0.0%)	0	

[1] Based on the comparison of the percentage of patients who experienced major or minor complications between the EVS and MC groups.

[2] The number of patients with a major complication or a specific type of major complication is equal to the number of major complication events. Each patient only experienced a given major complication once.

IX. Summary of Preclinical Studies

Bench and In-vitro Device Characterization Testing

1. Biocompatibility

Biocompatibility testing of the EVS™ Vascular Closure System was conducted in accordance with FDA's-modified matrix of ISO 10993-1, "Biological Evaluation of Medical Devices, Part 1 Evaluation and Testing". As seen in the Table 2 below, all testing passed and results concluded that the EVS™ Vascular Closure System is non-toxic and non-irritant.

Table 2: EVS™ Vascular Closure System Functional Test Table

Biocompatibility Test	Test Article	Result
ISO MEM Elution (L-929)	Dilator-Nylon 11; Transitional Sheath-Polyester PET; Titanium 3 AL 2.5V-staple Passivated and Non-Passivated; Mandrel Rod; Tube assemblies (PTFE coating), and Hydrophilic Coating	PASS
ISO Systemic Injection Test	Titanium 3 AL 2.5V-staple Passivated and Non-Passivated; Transitional Sheath-Polyester PET; Dilator-Nylon 11; Mandrel Rod; Hydrophilic Coating, and Tube assemblies (PTFE coating)	PASS
Hemolysis Rabbit Blood – ISO	Titanium 3 AL 2.5V-staple Passivated and Non-Passivated; Transitional Sheath-Polyester PET; Dilator-Nylon 11; Mandrel Rod; Hydrophilic Coating, and Tube assemblies (PTFE coating)	PASS
Rabbit Pyrogen Test (Materials Mediated) – ISO	Titanium 3 AL 2.5V-staple Passivated and Non-Passivated; Transitional Sheath-Polyester PET; Dilator-Nylon 11; Mandrel Rod; Hydrophilic Coating, and Tube assemblies (PTFE coating)	PASS
ISO Intracutaneous Injection Test	Titanium 3 AL 2.5V-staple Passivated and Non-Passivated; Transitional Sheath-Polyester PET; Dilator-Nylon 11; Mandrel Rod; Hydrophilic Coating, and Tube assemblies (PTFE coating)	PASS
ISO Intramuscular Implantation Test	Titanium 3 AL 2.5V-staple Passivated and Non-Passivated; Transitional Sheath-Polyester PET; Dilator-Nylon 11; Mandrel Rod; Hydrophilic Coating, and	PASS

	Tube assemblies (PTFE coating)	
ISO Kligman Maximization Test	Titanium 3 AL 2.5V-staple Passivated and Non-Passivated; Transitional Sheath-Polyester PET; Dilator-Nylon 11; Mandrel Rod; Hydrophilic Coating, and Tube assemblies (PTFE coating)	PASS

2. Functionality

In-vitro tests were conducted to characterize the mechanical performance of the EVS™ Vascular Closure System. Results from the mechanical tests demonstrated that the EVS™ Vascular Closure System performance was acceptable. See Table 2 for results.

Table 2: EVS™ Vascular Closure System Functional Test Table

EVS Vascular Closure System Device Capability Limits Testing Matrix		
Item	**Results/Acceptance Criteria**	**Safety Factor**
Introducer retention foot activated lock load limit	7.47 lbf. Avg. (5.06 lbf. Min) vs. Average retention load of 2.19 lbf.	3.4
Introducer retention foot to wire attachment strength	7.55 lbf. Avg. (6.05 lbf. Min) vs. Average retention load of 2.19 lbf.	3.4
Introducer retention foot grip capacity in vessel	2.19 lbf. Avg. (1.75 lbf. Min.)	N/A
Introducer retention foot to foot tube holder separation force	3.24 lbf. Avg. (3.02 lbf. Min) vs. negligible, unmeasurable force to overcome component friction during retention foot release	High
Stapler system drive-train and structural components capacity (handle, gears, pins, cam)	Maximum *tested* loading of 35 lbf. vs. Maximum functional load of 21 lbf.	> 1.7
Stapler mandrel rod ferrule crimp capacity limit	Minimum retention of 84 lbf. vs. Maximum load of 21 lbf.	4.0
Stapler mandrel weld strength limit	Minimum strength of 61 lbf. vs. Maximum load of 21 lbf.	2.9
Staple tip closure force capacity	1.42[1.00 @ 45°] lbf./leg Avg. (1.20 lbf. Min) vs. Closure requirement of .031 lbf./leg for Max. 250 mm Hg pressure retention	32
Staple closure capacity, pressure	310 mm Hg Min. (427 mm Hg Avg.) achieved vs. Required closure capacity of 250 mm Hg	Min. 1.2

3. Sterilization and Shelf Life

The EVS™ Vascular Closure System is packaged in a thermoformed tray with a Tyvek™ lid, labeled, and placed into a dispenser box. The dispenser box is then placed into a master carton. The EVS™ Vascular Closure System is sterilized using EtO. The device has been validated and approved for a 1-year shelf life.

X. Clinical Studies

The EVS™ Vascular Closure System was evaluated in a randomized, multi-center clinical investigation involving 362 patients within the United States. The EVS™ Vascular Closure System was compared to Manual Compression (MC) methods following interventional and diagnostic catheterization procedures. Prior to randomizing patients, each center enrolled a series of "non-randomized EVS™ Vascular Closure System run-in" patients to ensure operator familiarity with the device.

The study was conducted at 7 U.S. institutions from March 2003 to December 2003. The randomization ratio for this study was 2:1, EVS to MC. Of the 362 randomized patients, 243 were randomized to the EVS™ Vascular Closure System and 119 were randomized to the Manual Compression arm of the study. Of the patients randomized to the EVS™ Vascular Closure System, 118 (49%) were interventional and 125 (51%) were diagnostic. Of the patients randomized to Manual Compression, 56 (47%) were interventional and 63 (53%) were diagnostic.

The study was designed as a pivotal, prospective, multi-center, open label, randomized study. The purpose of this study was to evaluate the safety, efficacy, and ease of use of the EVS™ Vascular Closure System for use in Percutaneous Femoral Artery Closure (PFAC) compared to the use of MC. The study was designed as an equivalency trial for the 30-day primary safety endpoint of combined rate of major complications.

A. Assessment of Safety

Safety endpoints consisted of anticipated procedure-related complications and unanticipated adverse effects. Anticipated complications were divided into pre-defined major and minor complications, and other complications. **Major complications** were defined as ultrasound guided compression for vascular repair, vascular surgery, total vessel occlusion, retroperitoneal bleeding, uncontrolled bleeding requiring transfusion, dislodgement of the closure device into the artery (intraluminal staple delivery) requiring surgical intervention, groin related infection requiring intravenous (IV) antibiotics or extended hospitalization, new significant neuropathy in the ipsilateral lower extremity (severe nerve damage), and new ischemia in the leg where the device was deployed (defined as a class change of one or more in the Rutherford score). **Minor complications** were defined as uncontrolled bleeding not requiring transfusion, hematoma ($\geq$ 6cm), ecchymosis (> 3mm), dislodgement of the closure device into the artery (intraluminal staple delivery) not requiring surgical intervention, ipsilateral lower extremity arterial emboli, ipsilateral deep vein thrombosis, access site-related vessel laceration, access site wound dehiscence, localized access site infection treated with intramuscular or oral antibiotics, pseudoaneurysm not requiring treatment, pseudoaneurysm requiring thrombin injection, arteriovenous fistula, and ipsilateral pedal pulse diminished by 2 grades.

The primary safety assessment was a comparison of the combined rate of major complications in each study arm within the 30-day follow-up period.

Additional comparisons were also done of the major and minor complication rates at each of four time intervals (immediately after the procedure, at discharge from the cardiac catheterization laboratory, prior to hospital discharge, and at the Day 30 (± 7 days) visit). Other anticipated complications were listed. Unanticipated treatment-emergent adverse effects were summarized and listed by body system and preferred term.

B. Assessment of Efficacy

The primary effectiveness endpoints were time to hemostasis and time to ambulation. **Time to hemostasis** was defined as the time from staple delivery or application of manual compression to the time hemostasis (defined as complete cessation of bleeding to include any oozing) was achieved. **Time to ambulation** was defined as the time from staple delivery or application of manual compression to the time the subject could stand and walk at least 20 feet. Two secondary effectiveness endpoints (**time to device deployment** defined as time from the end of the catheterization procedure to device deployment or application of manual compression, and **time to hospital discharge**) were originally specified in the protocol and analysis plan. Two additional secondary effectiveness endpoints were added (**mean change in ACT level from the procedure end to device deployment**, and **time of device deployment** defined as time from sheath removal to device deployment or application of manual compression). The mean change in ACT level was added because it was considered clinically important. The time from sheath removal to device deployment was added to demonstrate how quickly the EVS™ device could be deployed. Other effectiveness assessments were **overall performance of device** (assessed by rates of procedural success, puncture site healing, device failures, and operator errors), **ease of use of the device**, and **overall assessment of device** (assessed by level of difficulty associated with device set up, device operation, staple deployment, and general function).

C. Inclusion and Exclusion Criteria:

1. Inclusion Criteria

In order to be included in the study, the patient must meet all of the following criteria:

- Undergo a percutaneous femoral access procedure for elective or urgent transfemoral cardiac or peripheral diagnostic or interventional catheterization
- Patients receiving chronic coumadin therapy are required to have a PT blood test within normal limits for the catheterization laboratory prior to study inclusion. Patients receiving continuous intravenous heparin infusions are required to have a PTT blood test below the upper limit of the institution's catheterization laboratory therapeutic range prior to study inclusion.
- If female, and of childbearing potential, have a negative serum HcG and not be lactating.
- Willing to sign the informed consent form, and
- Willing and available to return for all study-related follow up procedures.

2. Exclusion Criteria:

There were three separate occasions at which the subjects were screened and may have met criteria that would have excluded them from study participation:

a. prior to the diagnostic/interventional procedure
b. intra-procedure
c. post-procedure

Subjects must not have met any exclusion criteria to be considered eligible for the study.

Pre-Procedure Exclusion Criteria:

Prior to the cardiac or peripheral catheterization or revascularization procedure, subjects were excluded if they met any of the following criteria:

1. Participation in another investigation with potential to confound treatment or outcome
2. Age ≤ 18 or ≥ 80 years
3. Diagnosis of a pre-existing autoimmune disease
4. History of bleeding disorder/platelet disorder such as von Willebrand's Disease or hemophilia
5. Bilateral chronic ischemia identified by claudication and significant atherosclerotic disease at the site of, or immediately adjacent to the site of, sheath insertion as determined by screening femoral angiography
6. Thrombolytic therapy administered within 24 hours
7. Prior use of a closure device in ipsilateral CFA within 6 months
8. Prior femoral vascular surgery at the targeted site
9. Prior stent placement in the vicinity of the arterial puncture site
10. Pre-existing pseudoaneurysm at targeted site
11. Pre-existing arterio-venous fistula at targeted site
12. Pre-existing non-cardiac systemic disease or terminal illness
13. Pre-existing systemic or cutaneous infection
14. Pre-existing ipsilateral groin hematoma
15. Pre-procedure platelet count <100,000 10^3/uL or hematocrit <28%

Intra-Procedural Exclusion Criteria:

During the catheterization procedure, subjects were not eligible to continue in the study if any of the following criteria were met:

1. Obesity precluding access with a standard needle (i.e., Seldinger needle)
2. Difficulty attaining arterial access or needing multiple punctures for access
3. Failed single wall arterial puncture
4. Bleeding around sheath prior to sheath removal
5. Absent pedal pulses of either extremity
6. Use of Sheath <6 or >8 French (Fr)
7. Tortuous vascular anatomy with greater than 90° bends
8. Arterial access obtained in or near a vascular graft
9. Cardiogenic shock experienced during or immediately post-procedure
10. Severe peripheral vascular disease at access site arteriotomy
11. Procedural usage of Angiomax™ anticoagulant therapy

Post-Procedure Exclusion Criteria:

After the catheterization procedure, but prior to closure, subjects were not eligible to continue in the study if they met any of the following criteria:

1. Activated clotting time (ACT) Levels: for subjects receiving heparin anticoagulation alone and randomized to the EVS device, ACT > 315 seconds at time of sheath removal. ***(Note that this exclusion criterion was removed in Protocol Amendment 2, Section 10.1.1. and replaced with "reasonable and usual practice standards for ACT levels applied to vascular hemostasis devices at each institution.")***
2. ACT Levels: for subjects receiving glycoprotein IIb/IIIa receptor inhibitor drugs and heparin, if randomized to the EVS device, ACT > 263 seconds at time of sheath removal. ***(Note that this exclusion criterion was removed in Protocol Amendment 2, Section 10.1.1. and replaced with "reasonable and usual practice standards for ACT levels applied to vascular hemostasis devices at each institution.")***
3. ACT Levels: If randomized to Manual Compression, ACT >180 seconds at time of sheath removal. (For manual compression subjects, sheath removal was delayed until ACT levels were below 180 seconds.)
4. ACT Levels: If randomized to Manual Compression with IIb/IIIa inhibitors, ACT >180 seconds at time of sheath removal. (For manual compression subjects, sheath removal was delayed until ACT levels were below 180 seconds.)
5. Systolic blood pressure (SBP) < 90 mmHg after the procedure
6. Uncontrolled hypertension [SBP>160 mmHg, diastolic blood pressure (DBP) >90 mmHg], unresponsive to medications prior to closure
7. If randomized to device, subject is not eligible if the sheath was not removed within the cardiac catheterization laboratory

D. Methodology

The study enrolled subjects into two separate phases: run-in and randomization. Each center enrolled a series of "device run-in" subjects to provide training and ensure operator familiarity with the device. Run-in subjects signed informed consent and met all inclusion/exclusion criteria. After the Medical Monitor determined there were no safety concerns and the Sponsor determined the site had sufficient experience with the device, the site was authorized to enroll subjects into the randomization phase.

During the randomization phase, subjects who met the initial inclusion/exclusion criteria were randomized in a 2:1 ratio to receive either EVS or MC for percutaneous femoral artery closure. Treatment groups were balanced by block within a center. Subjects provided pre-procedural medical history, current medications, physical examination, and clinical laboratory results (hematocrit and platelets). When applicable, subjects provided PT, PTT/INR, and serum pregnancy tests. Among randomized subjects, the intent was to enroll approximately 50% undergoing diagnostic procedures and 50% undergoing interventional procedures.

Prior to the procedure, a subset of randomized subjects in each study arm agreed to undergo a femoral artery ultrasound. If, after catheterization but prior to closure, the subject remained eligible, percutaneous closure of the treatment femoral artery was performed using the procedure assigned at randomization. Any post-procedure complications (major, minor, or other), unexpected adverse effects, and concomitant medications were recorded at four time intervals: immediately after the procedure, at discharge from the cardiac catheterization laboratory, prior to hospital discharge, and at the Day 30 (±7 days) visit.

Subjects were evaluated for the time at which hemostasis was achieved. Subjects were asked to ambulate at pre-set time intervals. The time intervals varied depending on the study arm and presence/absence of IIb/IIIa inhibitors. The time from the procedure (device deployment or application of manual compression) to successful ambulation was recorded. Time to hospital discharge was also recorded.

Each investigator completed a questionnaire at the end of each procedure, to determine ease of use of the EVS™ compared to other closure devices, ease of operation, ease of staple deployment, and general function.

Subjects were asked to return to the study site at 30 days (±7 days) post-procedure. In addition to the assessments of complications and adverse effects, subjects who had an ultrasound prior to the procedure had a second femoral artery ultrasound.

E. Study Population

A total of 362 patients were enrolled in the trial, with 137 males (56.4%) and 106 females (43.6%) randomized to EVS, compared to 75 males (63.0%) and 44 females (37.0%) randomized to MC. The mean age of subjects randomized to EVS was 61.2 years; the mean age for subjects randomized to MC was 62.9 years. The majority of subjects were Caucasian: 197 (81.1%) randomized to EVS and 89 (74.8%) randomized to MC. The mean body mass index was identical for both randomized groups: 31.2 kg/m^2. Baseline vital signs were also similar or identical at baseline for the randomized groups: mean systolic blood pressure of 134.6 mmHg (EVS) and 138.8 mmHg (MC); mean diastolic blood pressure of 73.8 mmHg (EVS) and 76.9 mmHg (MC); heart rate of 72.4 (EVS) and 71.2 (MC); respiratory rate of 18.9 beats per minute for both groups, and a mean oral body temperature of 97.6°F (EVS) and 97.5°F (MC). Results for the "Per Protocol" population were similar to those for the "Intent To Treat" population. There were no significant differences between the two randomized groups with respect to gender, age, risk factors, body size, blood pressure, hematocrit, platelet count, and INR.

F. Safety Data

A summary of the adverse events (complications) experienced by patients enrolled in the EVS™ Vascular Closure System randomized, multi-center clinical study is reported in Table 1 on page 5, above. A major complication was experienced by 1 (0.4%) of 243 patients randomized to the EVS™ Vascular Closure System compared to 3 (2.5%) of the 119 patients randomized to Manual Compression.

Device failure occurred in 2 (0.8%) randomized EVS cases; both of which proceeded to successful closure without clinical sequelae despite device failure.

Operator error occurred in only 7 (2.9%) of the randomized EVS cases, with only one related to a major complication.

No deaths occurred in the EVS arm of the study. One death (myocardial infarction) occurred in the manual compression arm of the study during the 30-day follow-up period, but it was not associated with the arterial access closure.

G. Effectiveness Data

Summaries of the effectiveness data from the study are reported in Tables 3 – 7 on pages 13 – 15 below. The effectiveness of the EVS™ Vascular Closure System was evaluated using two primary endpoints: time to hemostasis and time to ambulation.

Use of EVS significantly reduced time to hemostasis and ambulation. The mean time to hemostasis was 4.4 minutes for randomized EVS patients, compared to 20.7 minutes for manual compression patients. The mean time to ambulation was 2.4 hours for randomized EVS patients compared to 6.0 hours for MC patients.

The procedural success rate (the percentage of patients achieving hemostasis within 20 minutes minus the percentage with any major complications) was significantly higher in randomized EVS patients (94.4%) compared to manual compression (72.9%). EVS could be readily deployed without evidence of an investigator learning curve. Satisfactory puncture site healing at 30 days was achieved by 98.8% of randomized EVS patients and 96.6% of manual compression patients.

The majority of investigators reported that the use of the EVS was easier or as easy to use as other marketed devices, and that they had no difficulty or insignificant difficulty with the device set-up, operation, deployment, and function.

Table 3: Descriptive Statistics for Effectiveness (ITT Population)

	Randomized EVS (N=243)	Randomized MC (N=119)	P-value
Time to hemostasis (minutes)			<0.0001[1]
N	222	116	
Mean (SD)	4.4 (4.1)	20.7 (8.0)	
Median	3.0	20.0	
Min-Max Range	0.0 – 25.0	2.0 – 62.0	
Time to ambulation (hours)			<0.0001[1]
N	214	103	
Mean (SD)	2.4 (3.3)	6.0 (5.2)	
Median	1.3	4.6	
Min-Max Range	0.8 – 24.2	2.9 – 44.5	
Time to Eligible Hospital Discharge (hours)			0.5382[1]
N	203	98	
Mean (SD)	20.1 (31.1)	18.1 (25.4)	
Median	8.5	6.6	
Min-Max Range	1.1 – 271.8	0.7 – 141.5	
Time to Actual Hospital Discharge (hours)			0.2053[1]
N	225	110	
Mean (SD)	23.0 (35.8)	19.0 (21.3)	
Median	13.6	9.5	
Min-Max Range	1.3 – 311.0	0.7 – 146.0	
Time from end of procedure to device deployment (minutes)			<0.0001[1]
N	243	118	
Mean (SD)	7.9 (21.4)	76.7 (110.5)	
Median	6.0	22.5	
Min-Max Range	0.0 – 330.0	0.0 – 723.0	
Time from sheath removal to device deployment (minutes)			<0.0001[1]
N	243	118	
Mean (SD)	1.3 (2 2)	0.2 (0.9)	
Median	1.0	0.0	
Min-Max Range	-2.0 – 16.0	0.0 – 6.0	

[1] p-value based on an unpaired t-test comparing randomized EVS and MC subjects.

Table 3a: Kaplan-Meier Estimates of Patients Achieving Effectiveness Endpoints

Endpoint	Post-Procedure Time Interval	Randomized EVS (N=243)		Randomized MC (N=119)		Log Rank P-value
		No. Achieving Endpoint	%	No. Achieving Endpoint	%	
Time to hemostasis (minutes)						<0.0001
	≤ 1 min	40	16.94%	0	0.00%	
	≤ 5 min	167	71.55%	2	1.69%	
	≤ 10 min	208	89.65%	7	5.93%	
	≤ 15 min	216	93.57%	22	18.64%	
	≤ 20 min	218	94.70%	89	75.42%	
Time to ambulation (hours)						<0.0001
	≤ 1hr	35	14.77%	0	0%	
	≤ 2 hours	156	66.30%	0	0%	
	≤ 3 hours	184	78.71%	1	0.89%	
	≤ 4 hours	194	83.24%	20	17.70%	
	≤ 5 hours	197	84.63%	68	60.18%	
Time to eligible hospital discharge (hours)						0.5517
	≤ 1hr	0	0%	1	0.85%	
	≤ 2 hours	16	6.78%	2	1.69%	
	≤ 3 hours	26	11.01%	4	3.39%	
	≤ 4 hours	50	21.23%	8	6.78%	
	≤ 5 hours	67	28.53%	29	25.23%	
	≤ 10 hours	105	45.10%	56	49.27%	
	≤ 24 hours	161	71.06%	81	74.01%	
Time to actual hospital discharge (hours)						0.7301
	≤ 1hr	0	0%	1	0.84%	
	≤ 2 hours	8	3.33%	1	0.84%	
	≤ 3 hours	19	7.93%	1	0.84%	
	≤ 4 hours	35	14.66%	2	1.69%	
	≤ 5 hours	58	24.33%	19	16.46%	
	≤ 10 hours	109	45.77%	56	48.66%	
	≤ 24 hours	162	68.86%	85	74.68%	

Table 4: Descriptive Statistics for Time to Hemostasis and Ambulation in Subjects Undergoing Diagnostic Procedures (ITT Population)

	Diagnostic Randomized EVS (N=125)	Diagnostic Randomized MC (N=63)	P-value
Time to hemostasis (minutes)			<0.0001[1]
N	116	63	
Mean (SD)	3.3 (2.6)	19.3 (5.7)	
Median	2.5	20.0	
Min-Max Range	0.0 – 15.0	2.0 – 43.0	
Time to ambulation (hours)			<0.0001[1]
N	112	55	
Mean (SD)	1.5 (1.1)	4.7 (2.2)	
Median	1.2	4.3	
Min-Max Range	0.8 – 7.6	2.9 – 20.0	

[1] p-value based on an unpaired t-test comparing randomized EVS and MC subjects.

Table 5: Descriptive Statistics for Time to Hemostasis and Ambulation in Subjects Undergoing Interventional Procedures (ITT Population)

	Interventional Randomized EVS (N=118)	Interventional Randomized MC (N=56)	P-value
Time to hemostasis (minutes)			<0.0001[1]
N	106	53	
Mean (SD)	5.5 (5.1)	22.3 (9.9)	
Median	4.0	20.0	
Min-Max Range	0.0 – 25.0	2.0 – 62.0	
Time to ambulation (hours)			0.0004[1]
N	102	48	
Mean (SD)	3.4 (4.5)	7.6 (7.0)	
Median	2.0	5.6	
Min-Max Range	0.9 – 24.2	3.4 – 44.5	

[1] p-value based on an unpaired t-test comparing randomized EVS and MC subjects.

Table 6: ACT level prior to Sheath Removal (ITT Population)

	Randomized EVS (N=243)	Randomized MC (N=119)	Randomized EVS Diagnostic (N=125)	Randomized MC Diagnostic (N=63)	Randomized EVS Interventional (N=118)	Randomized MC Interventional (N=56)
ACT level (seconds) prior to sheath removal						
N	241	115	123	61	118	54
Mean (SD)	182.7 (65.2)	142.8 (34.0)	137.0 (43.0)	126.7 (35.0)	230.4 (47.8)	161.1 (21.3)
Median	179.0	154.0	129.0	123.0	232.0	162.0
Min-Max Range	63.0 – 427.0	42.0 – 229.0	63.0 – 311.0	42.0 – 180.0	65.0 – 427.0	103.0 – 229.0

Table 7: Overall Performance of Device for all Sites (ITT Population)

	Randomized EVS (N=243)	Randomized MC (N=119)	p-value[1]
Procedural success			0.0001
Life-table estimate of hemostasis within 20 minutes [number of subjects]	94.7% [218]	75.4% [89]	
Minus major complication rate [number of subjects]	(0.4%) [1]	(2.5%) [3]	
Procedural success rate[2]	94.3%	72.9%	
Satisfactory puncture site healing (Day 30)			0.3971
Yes	240 (98.8%)	115 (96.6%)	
No	3 (1.2%)	3 (2 5%)	
Device failure			1.0000
Yes	2 (0.8%)	0 (0.0%)	
No	241 (99.2%)	119 (100.0%)	
Operator error			0.1008
Yes	7 (2.9%)	0 (0.0%)	
No	236 (97.1%)	119 (100.0%)	

[1] p-value based on Fisher's exact test comparing randomized EVS and MC subjects.
[2]The procedural success rate was defined as the percentage of subjects in the ITT population achieving hemostasis within 20 minutes minus the percentage with any major complications.

Even though the study was designed as an equivalency study for the safety endpoint and a superiority study for the efficacy endpoints, there were several notable differences between the study arms. First, a higher percentage of EVS™ subjects than MC subjects received anti-coagulant therapy both before and during the study; before the study, 49.4% of EVS subjects (120/243) received anti-coagulant therapy versus 39.5% (47/119) of MC subjects, while, during the study, 93.4% (227/243) of EVS subjects received anti-coagulant therapy compared to 90.8% (108/119) of MC subjects.

A second significant difference was in mean ACT levels at the time the procedural sheath was removed. EVS™ subjects had a mean ACT at sheath removal of 182.7 seconds compared to 142.8 seconds for the MC group. For randomized subjects undergoing interventional procedures, the difference was more dramatic: interventional randomized EVS subjects had a mean ACT level of 230.4 seconds prior to sheath removal, compared to a mean of 161.1 seconds for MC subjects. ACT levels were higher at the time of sheath removal for the EVS™ arm because the MC subjects had delayed sheath removal while waiting for ACT levels to drop to clinically safe levels. This difference impacted the time to device deployment. The mean time to device deployment for all randomized EVS subjects was 7.9 minutes compared to 76.7 minutes for all MC subjects. This difference was even more dramatic for interventional subjects. This means that despite a significantly higher ACT level at the time of sheath removal for the EVS™ subjects, these subjects were allowed to commence PFAC within minutes of the end of the procedure.

XI. Conclusions Drawn from Studies:

The results of the in-vitro (laboratory) testing and the clinical study together provide valid scientific evidence and reasonable assurance that the EVS™ Vascular Closure System is safe and effective when used in accordance with its labeling.

The safety of the device has been demonstrated by the fact that the incidence of major complications in the randomized clinical investigation was lower than the manual compression arm of the study. The effectiveness of the EVS™ Vascular Closure System was demonstrated by a significant reduction in time to hemostasis and time to ambulation in patients assigned to the EVS™ Vascular Closure System treatment compared to those assigned to manual compression.

XII. Panel Recommendation

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by the panel.

XIII. CDRH Decision

FDA issued a PMA approval order to *angio*LINK Corporation on November 3, 2004. FDA also performed an inspection of the manufacturing facilities and found the applicant in compliance with the Quality System Regulation (21 CFR Part 820).

XIV. Approval Specifications

A. Instructions for Use: See the labeling.

B. Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events sections of the labeling.

C. Post Approval Requirements and Restrictions: See approval order.